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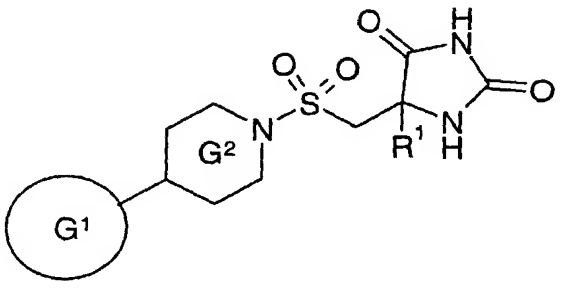

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(57) Abstract: The invention provides compounds of formula in which R^1, G^1 and G^2 have the meanings defined in the specification; processes for their preparation; pharmaceutical compositions containing them; a process for preparing the pharmaceutical compositions; and their use in therapy.

WO 2004/024718 A1

IMIDAZOLIDINEDIONE-DERIVATIVES AND THEIR USE AS METALLOPROTEINASE INHIBITORS.

The present invention relates to novel compounds, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

Metalloproteinases are a superfamily of proteinases (enzymes) whose numbers in recent years have increased dramatically. Based on structural and functional considerations these enzymes have been classified into families and subfamilies as described in N.M. Hooper (1994) FEBS Letters 354:1-6. Examples of metalloproteinases include the matrix metalloproteinases (MMPs) such as the collagenases (MMP1, MMP8, MMP13), the gelatinases (MMP2, MMP9), the stromelysins (MMP3, MMP10, MMP11), matrilysin (MMP7), metalloelastase (MMP12), enamelysin (MMP19), the MT-MMPs (MMP14, MMP15, MMP16, MMP17); the reprolysin or adamalysin or MDC family which includes the secretases and sheddases such as TNF converting enzymes (ADAM10 and TACE); the astacin family which include enzymes such as procollagen processing proteinase (PCP); and other metalloproteinases such as aggrecanase, the endothelin converting enzyme family and the angiotensin converting enzyme family.

Metalloproteinases are believed to be important in a plethora of physiological disease processes that involve tissue remodelling such as embryonic development, bone formation and uterine remodelling during menstruation. This is based on the ability of the metalloproteinases to cleave a broad range of matrix substrates such as collagen, proteoglycan and fibronectin. Metalloproteinases are also believed to be important in the processing, or secretion, of biological important cell mediators, such as tumour necrosis factor (TNF); and the post translational proteolysis processing, or shedding, of biologically important membrane proteins, such as the low affinity IgE receptor CD23 (for a more complete list see N. M. Hooper *et al.*, (1997) Biochem J. 321:265-279).

Metalloproteinases have been associated with many diseases or conditions. Inhibition of the activity of one or more metalloproteinases may well be of benefit in these diseases or conditions, for example: various inflammatory and allergic diseases such as, inflammation of the joint (especially rheumatoid arthritis, osteoarthritis and gout), inflammation of the gastro-intestinal tract (especially inflammatory bowel disease, ulcerative colitis and gastritis), inflammation of the skin (especially psoriasis, eczema, dermatitis); in tumour metastasis or invasion; in disease associated with uncontrolled degradation of the extracellular matrix such as osteoarthritis; in bone resorptive disease (such as osteoporosis and Paget's disease); in diseases associated with aberrant angiogenesis; the enhanced collagen remodelling associated with diabetes, periodontal disease (such as gingivitis), corneal ulceration, ulceration of the skin, post-operative conditions (such as colonic anastomosis) and dermal wound healing; demyelinating diseases of the central and peripheral nervous systems (such as multiple sclerosis); Alzheimer's disease; extracellular matrix remodelling observed in cardiovascular diseases such as restenosis and atheroscelerosis; asthma; rhinitis; and chronic obstructive pulmonary diseases (COPD).

MMP12, also known as macrophage elastase or metalloelastase, was initially cloned in the mouse by Shapiro *et al* [1992, Journal of Biological Chemistry 267: 4664] and in man by the same group in 1995. MMP12 is preferentially expressed in activated macrophages, and has been shown to be secreted from alveolar macrophages from smokers [Shapiro *et al*, 1993, Journal of Biological Chemistry, 268: 23824] as well as in foam cells in atherosclerotic lesions [Matsumoto *et al*, 1998, Am J Pathol 153: 109]. A mouse model of COPD is based on challenge of mice with cigarette smoke for six months, two cigarettes a day six days a week. Wildtype mice developed pulmonary emphysema after this treatment. When MMP12 knock-out mice were tested in this model they developed no significant emphysema, strongly indicating that MMP12 is a key enzyme in the COPD pathogenesis. The role of MMPs such as MMP12 in COPD (emphysema and bronchitis) is discussed in Anderson and Shinagawa, 1999, Current Opinion in Anti-inflammatory and Immunomodulatory Investigational Drugs 1(1): 29-38. It was recently discovered that

smoking increases macrophage infiltration and macrophage-derived MMP-12 expression in human carotid artery plaques Kangavari [Matetzky S, Fishbein MC *et al.*, Circulation 102:(18), 36-39 Suppl. S, Oct 31, 2000].

MMP9 (Gelatinase B; 92kDa TypeIV Collagenase; 92kDa Gelatinase) is a secreted protein which was first purified, then cloned and sequenced, in 1989 [S.M. Wilhelm *et al* (1989) J. Biol Chem. 264 (29): 17213-17221; published erratum in J. Biol Chem. (1990) 265 (36): 22570]. A recent review of MMP9 provides an excellent source for detailed information and references on this protease: T.H. Vu & Z. Werb (1998) (In : Matrix Metalloproteinases. 1998. Edited by W.C. Parks & R.P. Mecham. pp115 - 148. Academic Press. ISBN 0-12-545090-7). The following points are drawn from that review by T.H. Vu & Z. Werb (1998).

The expression of MMP9 is restricted normally to a few cell types, including trophoblasts, osteoclasts, neutrophils and macrophages. However, it's expression can be induced in these same cells and in other cell types by several mediators, including exposure of the cells to growth factors or cytokines. These are the same mediators often implicated in initiating an inflammatory response. As with other secreted MMPs, MMP9 is released as an inactive Pro-enzyme which is subsequently cleaved to form the enzymatically active enzyme. The proteases required for this activation *in vivo* are not known. The balance of active MMP9 versus inactive enzyme is further regulated *in vivo* by interaction with TIMP-1 (Tissue Inhibitor of Metalloproteinases -1), a naturally-occurring protein. TIMP-1 binds to the C-terminal region of MMP9, leading to inhibition of the catalytic domain of MMP9. The balance of induced expression of ProMMP9, cleavage of Pro- to active MMP9 and the presence of TIMP-1 combine to determine the amount of catalytically active MMP9 which is present at a local site. Proteolytically active MMP9 attacks substrates which include gelatin, elastin, and native Type IV and Type V collagens; it has no activity against native Type I collagen, proteoglycans or laminins.

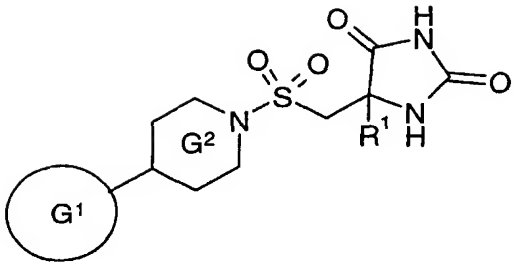
There has been a growing body of data implicating roles for MMP9 in various physiological and pathological processes. Physiological roles include the invasion of embryonic trophoblasts through the uterine epithelium in the early stages of embryonic implantation; some role in the growth and development of bones; and migration of inflammatory cells from the vasculature into tissues.

MMP9 release, measured using enzyme immunoassay, was significantly enhanced in fluids and in AM supernantants from untreated asthmatics compared with those from other populations [Am. J. Resp. Cell & Mol. Biol., Nov 1997, 17 (5):583-591]. Also, increased MMP9 expression has been observed in certain other pathological conditions, thereby implicating MMP9 in disease processes such as COPD, arthritis, tumour metastasis, Alzheimer's, Multiple Sclerosis, and plaque rupture in atherosclerosis leading to acute coronary conditions such as Myocardial Infarction.

A number of metalloproteinase inhibitors are known (see for example the reviews of MMP inhibitors by Beckett R.P. and Whittaker M., 1998, Exp. Opin. Ther. Patents, 8(3):259-282, and by Whittaker M. *et al*, 1999, Chemical Reviews 99(9):2735-2776).

We have now discovered a new class of compounds that are inhibitors of metalloproteinases and are of particular interest in inhibiting MMPs such as MMP12 and MMP9. In particular, we have discovered compounds that are potent dual MMP12 and MMP9 inhibitors and have desirable activity profiles. The compounds of this invention have beneficial potency, selectivity and/or pharmacokinetic properties.

In accordance with the present invention, there is therefore provided a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof



(I)

wherein

R^1 represents hydrogen, or a group selected from C_1-C_6 alkyl and a saturated or unsaturated 3- to 10-membered ring system which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each group being optionally substituted with at least one substituent selected from halogen, hydroxyl, cyano, carboxyl, $-NR^2R^3$, $-CONR^4R^5$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylcarbonyl(oxy), $-S(O)_mC_1$-C_6 alkyl where m is 0, 1 or 2, C_1-C_6 alkylsulphonylamino, C_1-C_6 alkoxycarbonyl(amino), benzyloxy and a saturated or unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring in turn being optionally substituted with at least one substituent selected from halogen, hydroxyl, oxo (=O), carboxyl, cyano, C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl and C_1-C_6 hydroxyalkyl;

R^2, R^3, R^4 and R^5 each independently represent hydrogen or C_1-C_6 alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy;

G^2 represents a piperidine or a tetrahydropyridine ring;

G^1 represents a 5- or 6- membered aryl or heteroaryl monocyclic ring which may be optionally fused to a second ring to form a bicyclic ring system containing a total of 8- to 10-ring atoms, the monocyclic ring or fused bicyclic ring system being optionally substituted with at least one substituent selected from halogen, hydroxyl, cyano, nitro, C_1-C_6 alkyl (optionally substituted by one or more of cyano, halogen, hydroxyl and methoxy), C_2-C_6 alkenyl, C_1-C_6 alkoxy (optionally substituted by one or more halogen atoms), $-S(O)_nC_1$-C_6 alkyl where n is 0, 1 or 2 (optionally substituted by one or more halogen atoms), C_1-C_6 alkylcarbonyl(amino), C_1-C_6 alkylcarbonyloxy, phenyl, benzyloxy and $-NR^6R^7$; and

R^6 and R^7 each independently represent hydrogen or C_1-C_6 alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy.

In the context of the present specification, unless otherwise stated, an alkyl or alkenyl substituent group or an alkyl moiety in a substituent group may be linear or branched. A hydroxyalkyl substituent may contain one or more hydroxyl groups but preferably contains one or two hydroxyl groups. In the definition of R^1, it should be understood that each of the saturated or unsaturated 3- to 10-membered ring system and the saturated or unsaturated 5- to 6-membered ring may have alicyclic or aromatic properties. An unsaturated ring system will be partially or fully unsaturated. Further, in G^1, the second ring in the bicyclic ring system need not be aromatic and may contain one or more ring heteroatoms selected from nitrogen, oxygen and sulphur.

In an embodiment of the invention, R^1 represents hydrogen, or a group selected from C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) and a saturated or unsaturated 3- to 10-membered ring system which may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur,
each group being optionally substituted with at least one substituent (e.g. one, two, three or four substituents independently) selected from halogen (e.g. chlorine, fluorine, bromine or iodine), hydroxyl, cyano, carboxyl, $-NR^2R^3$, $-CONR^4R^5$, C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C_1-C_6, preferably C_1-C_4, alkylcarbonyl(oxy) (e.g. methylcarbonyl(oxy), ethylcarbonyl(oxy), n-propylcarbonyl(oxy), isopropylcarbonyl(oxy), n-butylcarbonyl(oxy), n-pentylcarbonyl(oxy) or n-hexylcarbonyl(oxy)), $-S(O)_mC_1$-C_6, preferably C_1-C_4, alkyl where m is 0, 1 or 2 (e.g. methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, methylsulphonyl or ethylsulphonyl), C_1-C_6, preferably C_1-C_4, alkylsulphonylamino (e.g. methylsulphonylamino, ethylsulphonylamino, n-propylsulphonylamino,

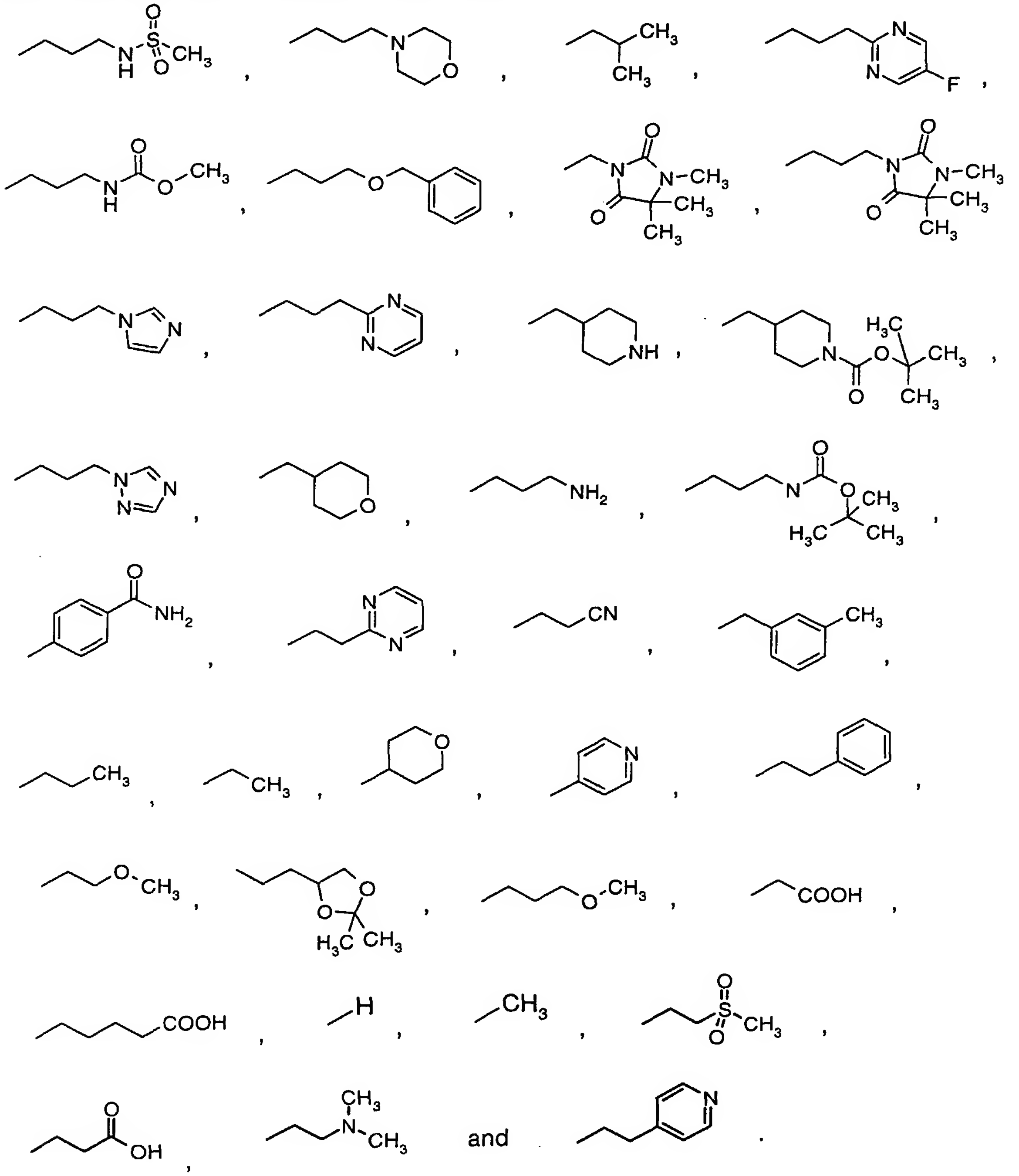
isopropylsulphonylamino, n-butylsulphonylamino, n-pentylsulphonylamino or n-hexylsulphonylamino), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl(amino) (e.g. methoxycarbonyl(amino), ethoxycarbonyl(amino), n-propoxycarbonyl(amino) or n-butoxycarbonyl(amino)), benzyloxy and a saturated or unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, the ring in turn being optionally substituted with at least one substituent (e.g. one, two or three substituents independently) selected from halogen (e.g. chlorine, fluorine, bromine or iodine), hydroxyl, oxo, carboxyl, cyano, C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl) and C_1-C_6, preferably C_1-C_4, hydroxyalkyl (e.g. $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$ or $-CH(OH)CH_3$).

Examples of saturated or unsaturated 3- to 10-membered ring systems that may be used, which may be monocyclic or polycyclic (e.g. bicyclic) in which the two or more rings are fused, include one or more (in any combination) of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl, cyclopentenyl, cyclohexenyl, phenyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, diazabicyclo[2.2.1]hept-2-yl, naphthyl, benzofuranyl, benzothienyl, benzodioxolyl, quinolinyl, 2,3-dihydrobenzofuranyl, tetrahydropyranyl, pyrazolyl, pyrazinyl, thiazolidinyl, indanyl, thienyl, isoxazolyl, pyridazinyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, indolyl, imidazolyl, pyrimidinyl, benzimidazolyl, triazolyl, tetrazolyl and pyridinyl. Preferred ring systems include phenyl, pyridinyl and tetrahydropyranyl.

Examples of saturated or unsaturated 5- to 6-membered ring substituents in R^1 include cyclopentyl, cyclohexyl, phenyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, thiomorpholinyl, pyrazolyl, pyrazinyl, pyridazinyl, thiazolidinyl, thienyl, isoxazolyl, pyrimidinyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, imidazolyl,

triazolyl, tetrazolyl and pyridinyl. Preferred rings include morpholinyl, pyrimidinyl, phenyl, imidazolyl, piperidinyl, tetrahydropyranyl and triazolyl.

Particular values for R^1 include the following:



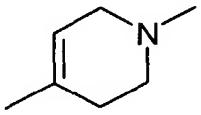
In another embodiment of the invention, R^1 represents hydrogen, or a group selected from C_1-C_4 alkyl and a saturated or unsaturated 5- to 10-membered ring system which may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur,
each group being optionally substituted with at least one substituent (e.g. one, two, three or four substituents independently) selected from halogen, hydroxyl, cyano, carboxyl, $-NR^2R^3$, $-CONR^4R^5$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylcarbonyl(oxy), $-S(O)_mC_1$-C_4 alkyl where m is 0, 1 or 2, C_1-C_4 alkylsulphonylamino, C_1-C_4 alkoxycarbonyl(amino), benzyloxy and a saturated or unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, the ring in turn being optionally substituted with at least one substituent (e.g. one, two or three substituents independently) selected from halogen, hydroxyl, oxo, carboxyl, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxycarbonyl and C_1-C_4 hydroxyalkyl.

In still another embodiment, R^1 represents hydrogen or C_1-C_4 alkyl, particularly methyl.

R^2, R^3, R^4 and R^5 each independently represent hydrogen or C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by at least one substituent (e.g. one, two or three substituents independently) selected from hydroxyl, halogen (e.g. chlorine, fluorine, bromine or iodine) and C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy).

In an embodiment of the invention, R^2, R^3, R^4 and R^5 each independently represent hydrogen or C_1-C_6, preferably C_1-C_4, alkyl, in particular methyl. In another embodiment, R^2, R^3, R^4 and R^5 each independently represent hydrogen.

G^2 represents piperidine or tetrahydropyridine such as 1,2,3,6-tetrahydropyridine of formula

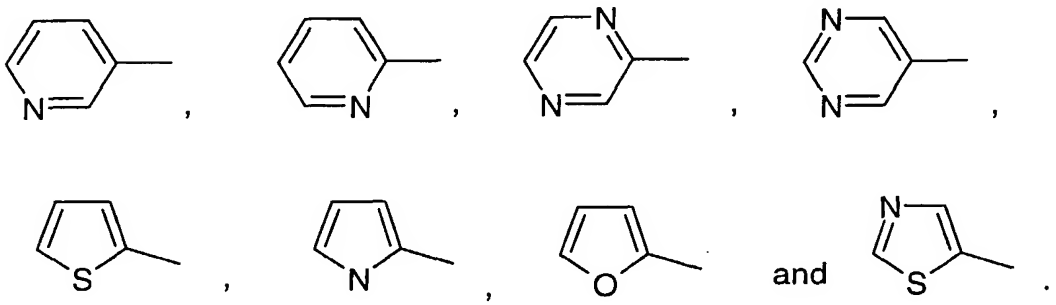


G^1 represents a 5- or 6- membered aryl or heteroaryl monocyclic ring which may be optionally fused to a second ring to form a bicyclic ring system containing a total of 8- to 10-ring atoms, the monocyclic ring or fused bicyclic ring system being optionally substituted with at least one substituent (e.g. one, two, three or four substituents independently) selected from halogen (e.g. chlorine, fluorine, bromine or iodine), hydroxyl, cyano, nitro, C_1-C_6, preferably C_1-C_4, alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl (optionally substituted by one or more, e.g. one, two or three, substituents independently selected from cyano, halogen such as chlorine, fluorine, bromine or iodine, hydroxyl and methoxy, e.g. $-CF_3$),
C_2-C_6, preferably C_2-C_4, alkenyl (e.g. ethenyl, prop-1-enyl, prop-2-enyl, but-1-enyl, pent-1-enyl, hex-1-enyl or 2-methyl-pent-2-enyl),
C_1-C_6, preferably C_1-C_4, alkoxy such as methoxy, ethoxy, n-propoxy or n-butoxy (optionally substituted by one or more, e.g. one, two or three, halogen atoms such as chlorine, fluorine, bromine or iodine, e.g. $-OCF_3$),
$-S(O)_nC_1$-C_6, preferably C_1-C_4, alkyl where n is 0, 1 or 2 (optionally substituted by one or more, e.g. one, two or three, halogen atoms such as chlorine, fluorine, bromine or iodine) (e.g. methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, methylsulphonyl, ethylsulphonyl or $-SCF_3$);
C_1-C_6, preferably C_1-C_4, alkylcarbonyl(amino) (e.g. methylcarbonyl(amino), ethylcarbonyl(amino), n-propylcarbonyl(amino), isopropylcarbonyl(amino), n-butylcarbonyl(amino), n-pentylcarbonyl(amino) or n-hexylcarbonyl(amino)),

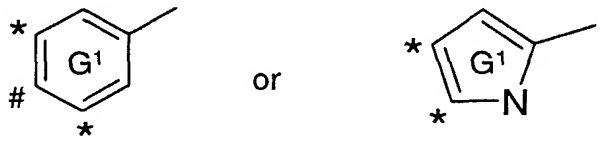
C_1-C_6, preferably C_1-C_4, alkylcarbonyloxy (e.g. methylcarbonyloxy, ethylcarbonyloxy, n-propylcarbonyloxy, isopropylcarbonyloxy, n-butylcarbonyloxy, n-pentylcarbonyloxy or n-hexylcarbonyloxy),
phenyl, benzyloxy and $-NR^6R^7$.

A 5- or 6-membered heteroaryl ring will comprise at least one ring heteroatom (e.g. one, two or three ring heteroatoms independently) selected from nitrogen, oxygen and sulphur.

Examples of 5- or 6- membered aryl or heteroaryl monocyclic rings include phenyl, pyridinyl, thienyl, furanyl, pyrazinyl, pyrimidinyl, pyrrolyl and thiazolyl, for instance,



If the 5- or 6- membered aryl or heteroaryl monocyclic ring is substituted, it is preferred that the substituent(s) are located in the *meta* and/or *para* positions, as illustrated in the examples below:



* denotes a *meta* substitution position; # denotes a *para* substitution position.

A preferred *meta* substituent is a C_1-C_3 alkyl group or $-CH_2CN$.
A preferred *para* substituent is Br, Cl, -CN, $-CF_3$, $-SCF_3$ or $-OCF_3$.

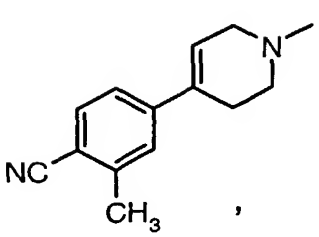
In an embodiment of the invention, in G^1, the 5- or 6- membered aryl or heteroaryl monocyclic ring is fused to a second ring to form a bicyclic ring system containing a total of 8- to 10-ring atoms such as quinolinyl, isoquinolinyl, indolyl, tetrahydroisoquinolinyl, benzofuranyl, dihydrobenzofuranyl, naphthyl or dihydroindolyl. A preferred bicyclic ring system is dihydrobenzofuranyl.

In one embodiment, G^1 represents a 5- or 6- membered aryl or heteroaryl monocyclic ring which may be optionally fused to a second ring to form a bicyclic ring system containing a total of 8- to 10-ring atoms, the monocyclic ring or fused bicyclic ring system being optionally substituted with one, two or three substituents independently selected from halogen, hydroxyl, cyano, nitro, C_1-C_4 alkyl (optionally substituted by one or more, e.g. one, two or three, substituents independently selected from cyano, halogen, hydroxyl and methoxy), C_2-C_4 alkenyl, C_1-C_4 alkoxy (optionally substituted by one or more, e.g. one, two or three, halogen atoms), $-S(O)_nC_1$-C_4 alkyl where n is 0, 1 or 2 (optionally substituted by one or more, e.g. one, two or three, halogen atoms), C_1-C_4 alkylcarbonyl(amino), C_1-C_4 alkylcarbonyloxy, phenyl, benzyloxy and $-NR^6R^7$.

In another embodiment, G^1 represents a 6- membered aryl or heteroaryl monocyclic ring which may be optionally fused to a second ring to form a bicyclic ring system containing a total of 9- to 10-ring atoms, the monocyclic ring or fused bicyclic ring system being optionally substituted with one or two substituents independently selected from halogen, cyano and C_1-C_4 alkyl.

In still another embodiment, G^1 represents phenyl, pyridinyl or dihydrobenzofuranyl, each of which is optionally substituted with one or two substituents independently selected from halogen (particularly chlorine), cyano and C_1-C_4 alkyl (particularly methyl).

Particular combinations of G^1 and G^2 include the following:



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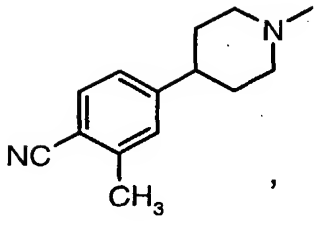

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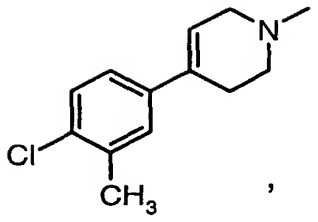

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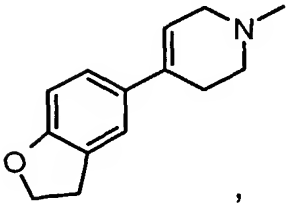

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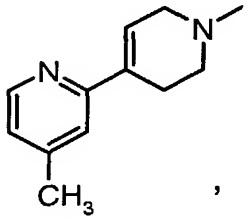

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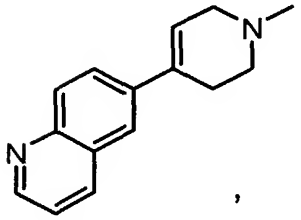

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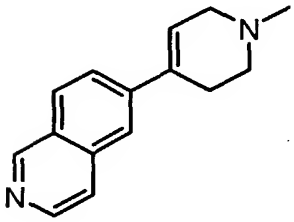

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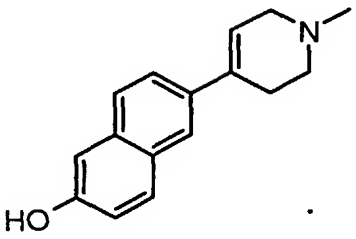


.

R^6 and R^7 each independently represent hydrogen or C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by at least one substituent (e.g. one, two or three substituents independently) selected from hydroxyl, halogen (e.g. chlorine, fluorine, bromine or iodine) and C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy).

In an embodiment of the invention, R^6 and R^7 each independently represent hydrogen or C_1-C_6, preferably C_1-C_4, alkyl, in particular methyl. In another embodiment, R^6 and R^7 each independently represent hydrogen.

In an embodiment of the invention:

R^1 represents C_1-C_4 alkyl;

G^2 represents a piperidine or a tetrahydropyridine ring; and

G^1 represents a 6- membered aryl or heteroaryl monocyclic ring which may be optionally fused to a second ring to form a bicyclic ring system containing a total of 9- to 10-ring atoms, the monocyclic ring or fused bicyclic ring system being optionally substituted with one or two substituents independently selected from halogen, cyano and C_1-C_4 alkyl.

In another embodiment of the invention:

R^1 represents methyl;

G^2 represents a piperidine or a tetrahydropyridine ring; and

G^1 represents phenyl, pyridinyl or dihydrobenzofuranyl, each of which is optionally substituted with one or two substituents independently selected from chlorine, cyano and methyl.

Examples of compounds of the invention include:

2-Methyl-4-[1-({[(4*S*)-4-methyl-2,5-dioxoimidazolidin-4-yl]methyl}sulfonyl)-1,2,3,6-tetrahydropyridin-4-yl]benzonitrile,

(5*S*)-5-({[4-(2,3-Dihydro-1-benzofuran-5-yl)-3,6-dihydropyridin-1(2*H*)-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione,

(5*S*)-5-Methyl-5-{[(4-methyl-3',6'-dihydro-2,4'-bipyridin-1'(2'*H*)-yl)sulfonyl]methyl}imidazolidine-2,4-dione,

(5*S*)-5-({[4-(4-Chloro-3-methylphenyl)-3,6-dihydropyridin-1(2*H*)-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione,

2-Methyl-4-[1-({[(4*S*)-4-methyl-2,5-dioxoimidazolidin-4-yl]methyl}sulfonyl)piperidin-4-yl]benzonitrile,

and pharmaceutically acceptable salts and solvates thereof.

It will be appreciated that the particular substituents and number of substituents in the compounds of the invention are selected so as to avoid sterically undesirable combinations.

Each exemplified compound represents a particular and independent aspect of the invention.

It will be appreciated that the compounds according to the invention may contain one or more asymmetrically substituted carbon atoms. The presence of one or more of these asymmetric centres (chiral centres) in compounds according to the invention can give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers and diastereomers, and mixtures including racemic mixtures thereof. Racemates may be separated into individual optically active forms using known procedures (cf. Advanced Organic Chemistry: 3rd Edition: author J March, p104-107) including for example the formation of diastereomeric derivatives having convenient optically active auxiliary species followed by separation and then cleavage of the auxiliary species.

Where optically active centres exist in the compounds of the invention, we disclose all individual optically active forms and combinations of these as individual specific embodiments of the invention, as well as their corresponding racemates.

Where tautomers exist in the compounds of the invention, we disclose all individual tautomeric forms and combinations of these as individual specific embodiments of the invention.

The compounds of the invention may be provided as pharmaceutically acceptable salts or solvates. These include acid addition salts such as hydrochloride, hydrobromide, citrate, tosylate and maleate salts and salts formed with phosphoric and sulphuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, or organic amine salt for example triethylamine. Examples of solvates include hydrates.

The compounds of formula (I) have activity as pharmaceuticals. As previously outlined the compounds of the invention are metalloproteinase inhibitors, in particular they are dual inhibitors of MMP12 and MMP9 and may be used in the treatment of diseases or conditions mediated by MMP12 and/or MMP9 such as asthma, rhinitis, chronic obstructive pulmonary diseases (COPD), arthritis (such as rheumatoid arthritis and osteoarthritis), atherosclerosis and restenosis, cancer, invasion and metastasis, diseases involving tissue destruction, loosening of hip joint replacements, periodontal disease, fibrotic disease, infarction and heart disease, liver and renal fibrosis, endometriosis, diseases related to the weakening of the extracellular matrix, heart failure, aortic aneurysms, CNS related diseases such as Alzheimer's disease and Multiple Sclerosis (MS), and hematological disorders.

In the context of the present specification, a compound is considered to be a dual inhibitor of MMP12 and MMP9 if the potency of the compound (as measured by its IC_{50} value) is less than or equal to 100 nanomolar ($\leq$ 100 nm) for each of MMP12 and MMP9, or, if the ratio of the potencies (MMP9:MMP12) is less than or equal to 20 ($\leq$ 20).

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention further provides a method of treating a disease or condition mediated by MMP12 and/or MMP9 which comprises administering to a patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as hereinbefore defined.

The invention also provides a method of treating an obstructive airways disease (e.g. asthma or COPD) which comprises administering to a patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. The daily dosage of the compound of formula (I)/salt/solvate (active ingredient) may be in the range from 0.001 mg/kg to 75 mg/kg, in particular from 0.5 mg/kg to 30 mg/kg. This daily dose may be given in divided doses as necessary. Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.10 to 70 %w, of active ingredient, and, from 1 to 99.95 %w, more preferably from 30 to 99.90 %w, of a pharmaceutically acceptable adjuvant, diluent or carrier, all percentages by weight being based on total composition.

Thus, the present invention also provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as hereinbefore defined in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

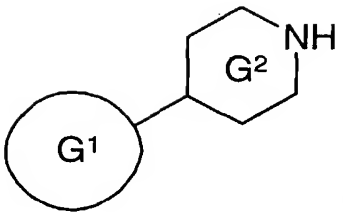
The pharmaceutical compositions of this invention may be administered in standard manner for the disease or condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal adminstration or by inhalation. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain, or be co-administered (simultaneously or sequentially) with, one or more pharmacological agents of value in treating one or more diseases or conditions referred to hereinabove such as "Symbicort" (trade mark) product.

Preparation of the compounds of the invention

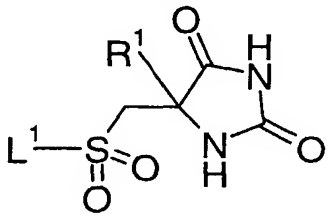
The present invention further provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as defined above which comprises,

(a) reacting a compound of formula



(II)

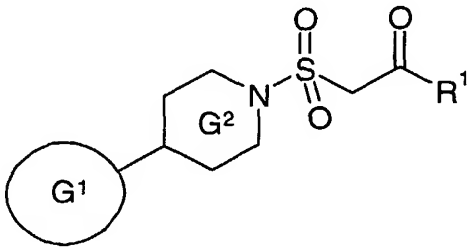
in which G^1 and G^2 are as defined in formula (I), with a compound of formula



(III)

wherein L^1 represents a leaving group (e.g. a halogen atom such as chlorine) and R^1 is as defined in formula (I); or

(b) reacting a compound of formula



(IV)

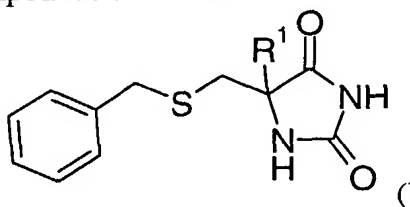
wherein R^1, G^1 and G^2 are as defined in formula (I), with potassium cyanide and ammonium carbonate;

and optionally after (a) or (b) forming a pharmaceutically acceptable salt or solvate.

In process (a), the reaction is conveniently carried in an organic solvent such as pyridine, dimethylformamide, tetrahydrofuran, acetonitrile or dichloromethane and optionally in the presence of a base such as triethylamine, N-methylmorpholine, pyridine or an alkali metal carbonate. The reaction will usually be carried out over about 1 to 24 hours at elevated temperature, for example, from ambient (20°C) to reflux temperature.

Compounds of formula (II) are either commercially available, are known in the literature (for example, from Wusttow *et al.*, *Synthesis*, 1991, 11, 993-995) or may be prepared using known techniques.

Compounds of formula (III) may be prepared as described by Mosher, J., *J. Org. Chem.*, 23, 1257 (1958), or alternatively, when L^1 represents chlorine, may be prepared by oxidative chlorination of compounds of formula

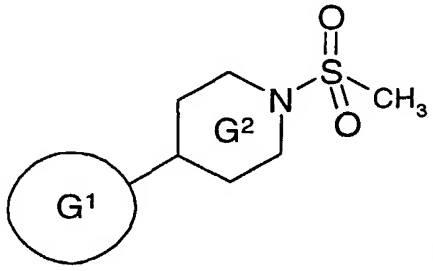


(V)

wherein R^1 is as defined in formula (III), for example, as described by Griffith, O.W., *J. Biol. Chem.*, 1983, 258 (3), 1591-1598.

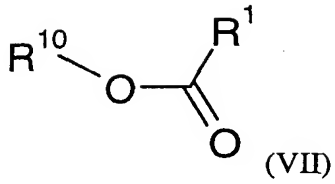
In process (b), the reaction is conveniently carried out in the presence of a protic solvent such as ethanol and in a sealed vessel at about 40°C to 80°C for about 4-24 hours.

Compounds of formula (IV) may conveniently be prepared by treating a compound of formula



(VI)

in which G^1 and G^2 are as defined in formula (IV) with excess (e.g. 2-3 equivalents worth) strong base such as lithium diisopropylamide, lithium hexamethyldisilazane or butyl lithium in the presence of an organic solvent such as tetrahydrofuran, followed by reaction with a compound of formula



(VII)

wherein R^{10} represents an alkyl or aryl group and R^1 is as defined in formula (IV), in a non-protic solvent.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of the invention may involve, at various stages, the addition and removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1999).

Compounds of formulae (V), (VI) and (VII) are either commercially available, are known in the literature or may be prepared using known techniques.

The present invention will now be further explained by reference to the following illustrative examples.

General procedures

^{1}HNMR and ^{13}CNMR were recorded on a Varian *unity Inova* 400 MHz or a Varian *Mercury*-VX 300 MHz instrument. The central peaks of chloroform-*d* (δ_H 7.27ppm), dimethylsulfoxide-d_6 (δ_H 2.50 ppm) or methanol-d_4 (δ_H 3.31 ppm) where used as internal references. Low-resolution mass spectra were obtained on an Agilent 100 LC-MS system

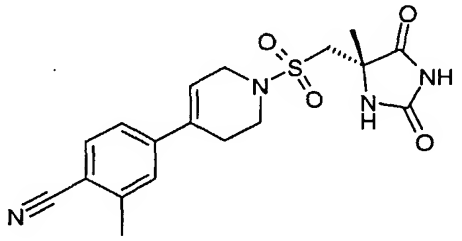
equipped with an APCI ionisation chamber. Column chromatography was carried out using silica gel (0.063-0.2 mm) (Merck). Unless stated otherwise, starting materials were commercially available. All solvents and commercial reagents were laboratory grade and used as received.

Abbreviations:

DCM: : dichloromethane
THF: tetrahydrofuran
LDA: lithium diisopropylamide
EtOAc: ethyl acetate
EtOH: ethanol
AcOH: acetic acid
Pd/C: palladium on carbon catalyst

Example 1

2-Methyl-4-[1-({[(4*S*)-4-methyl-2,5-dioxoimidazolidin-4-yl]methyl}sulfonyl)-1,2,3,6-tetrahydropyridin-4-yl]benzonitrile



2-Methyl-4-(1,2,3,6-tetrahydropyridin-4-yl)benzonitrile; hydrochloride (60 mg, 0.26 mmol) was taken up in 2 ml of dry DCM and 2 ml of dry THF and neutralised with diisopropylethylamine (55 µl, 0.33 mmol) at room temperature. [(4*S*)-4-Methyl-2,5-dioxo-imidazolodin-4-yl]methanesulfonyl chloride (80 mg, 0.35 mmol) was added and after stirring for 10 min, diisopropylethylamine (55 µl, 0.33 mmol) was added and the reaction mixture was stirred at room temperature until LC-MS (APCI) indicated consumption of the

amine. The reaction mixture was evaporated and the residue was purified using preparative HPLC to give the title compound (yield = 27 mg, 27%).

LC-MS (APCI) m/z 389 [MH^+].

^{1}H NMR (DMSO-d_6): δ 10.76 (1H, s); 8.04 (1H, s); 7.74 (1H, d, *J*=8.07 Hz); 7.56 (1H, s); 7.46 (1H, d, *J*=8.07 Hz); 6.40 (1H, s); 3.90 (2H, q, *J*=3.07 Hz); 3.55, 3.42 (1H each, ABq, *J*=14.79 Hz); 3.39 (2H, t, *J*=5.92 Hz); 2.59 (2H, bs); 2.50 (obscured by DMSO-peak) (3H, s); 1.34 (3H, s).

The starting materials were prepared as follows:

tert-Butyl 4-{[(trifluoromethyl)sulfonyl]oxy}-3,6-dihydropyridine-1(2H)-carboxylate

A solution of tert-butyl 4-oxopiperidine-1-carboxylate (5.07 g, 25mmol) in THF (50 ml) was added drop wise to a solution of LDA (2M in THF, 15 ml, 30mmol) and THF (100 ml) over 25 mins at –78 °C. After stirring for 10 mins a solution of 1,1,1-trifluoro-N-phenyl-N-[(trifluoromethyl)sulfonyl]methanesulfonamide (10g, 28 mmol) in THF (50ml) was added and the mixture stirred at 0 °C for 3 hours. The solvent was evaporated off and the residue passed through a 20 g plug of aluminium oxide with 9:1 heptane / ethyl acetate. The solvent was evaporated to give 7.5 g product.

GC/MS m/z: 331 [M^+] very weak.

^{1}H NMR ($CDCl_3$): δ 1.47 (9H, s); 2.41-2.47 (2H, m); 3.63 (2H, t); 4.04 (2H, q); 5.76 (1H, bs).

tert-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate

tert-Butyl 4-{[(trifluoromethyl)sulfonyl]oxy}-3,6-dihydropyridine-1(2H)-carboxylate (7.50g, 22.6 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (6.33 g, 24.9mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) (55 mg, 0.7mmol), 1,1'-bis(diphenylphosphino)ferrocene (37 mg, 0.7 mmol) and potassium acetate

(6.6 g, 67mmol) were mixed, reaction vessel purged with nitrogen and heated at 80 °C for 6 hours. The solvent was evaporated and the residue purified by column chromatography eluting with 9 heptane :1 ethyl acetate to give 4.4 g product.

^{1}H NMR ($CDCl_3$): δ 1.26 (12H, s); 1.46 (9H, s); 2.19-2.25 (2H, m); 3.43 (2H, t); 3.94 (2H, q); 6.44-6.48 (1H, m).

tert-Butyl 4-(4-cyano-3-methylphenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate

4-Bromo-2-methyl-benzonitrile (150 mg, 0.77 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (284 mg, 0.92 mmol) and $PdCl_2$(dppf) (38 mg, 0.05 mmol) were dissolved in toluene (2.5 ml), EtOH (0.75 ml) and 2M aqueous Na_2CO_3. The reaction vessel was purged with nitrogen and heated at 80 °C over night. After cooling, the mixture was partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried over Na_2SO_4 and purified using flash chromatography (heptane:ethylacetate 7:1) affording 171 mg (74%) of white crystals.

LC-MS m/z 199 [M^+].

^{1}H NMR ($CDCl_3$): δ 7.52 (1H, d, *J*=8.09 Hz); 7.27 (1H, s); 7.23 (1H, d, *J*=8.51 Hz); 6.12 (1H, bs); 4.07 (2H, q, *J*=5.81 Hz); 3.61 (2H, t, *J*=5.61 Hz); 2.52 (3H, s); 2.48 (2H, bs); 1.47 (9H, s).

2-Methyl-4-(1,2,3,6-tetrahydropyridin-4-yl)benzonitrile hydrochloride

tert-Butyl 4-(4-cyano-3-methylphenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (110 mg, 0.37 mmol) was dissolved in THF (5 ml) and conc. HCl (5 ml) and was stirred at room temperature for 30 minutes after which the solvents were removed by rotary evaporation. The residue was dissolved in EtOH and toluene and evaporated again twice to remove all traces of water affording 84 mg (97%) of the title product.

LC-MS (APCI) m/z 199 [MH^+].

5-Methyl-5-{[(phenylmethyl)thio]methyl}imidazolidine-2,4-dione

A steel vessel was charged with ethanol and water (315mL/135mL).

31.7g (0.175 mol) of benzylthioacetone, 22.9g (0.351 mol) of potassium cyanide and 84.5g (0.879 mol) of ammonium carbonate was added. The closed reaction vessel was kept in an oil bath (bath temperature 90 °C) under vigorous stirring for 3h. The reaction vessel was cooled with ice-water (0.5 h), the yellowish slurry was evaporated to dryness and the solid residue partitioned between 400 mL water and 700 mL ethylacetate and separated. The water-phase was extracted with ethyl acetate (300 mL). The combined organic phases were washed with saturated brine (150 mL), dried (Na_2SO_4), filtered and evaporated to dryness. If the product did not crystallize, 300 mL of dichloromethane was added to the oil. Evaporation gave the product as a slightly yellowish powder,43.8 g (90%).

LC-MS (APCI) m/z 251.1 (MH+).

^{1}H NMR (DMSO-d_6) δ: 10.74 (1H,s); 8.00 (1H, s); 7.35-7.20 (5H, m); 3.76 (2H, s); 2.72, 2.62 (1H each, ABq, *J*=14.0 Hz); 1.29 (3H, s).

^{13}C NMR (DMSO-d_6) δ: 177.30, 156.38, 138.11, 128.74, 128.24, 126.77, 62.93, 37.96, 36.39, 23.15.

(5*S*)-5-Methyl-5-{[(phenylmethyl)thio]methyl}imidazolidine-2,4-dione

The title compound was prepared by chiral separation of the racemic material using a 250mm x 50mm column on a Dynamic Axial Compression Preparative HPLC system. The stationary phase used was CHIRALPAK AD, eluant=Methanol, flow=89mL/min, temp=ambient, UV=220nm, sample conc=150mg/mL, injection volume=20mL.

Retention time for title compound = 6 min.

Analysis of chiral purity was made using a 250mm x 4.6mm CHIRALPAK-AD column from Daicel, flow=0.5mL/min, eluent=Ethanol, UV=220nm, temp=ambient.

Retention time for title compound = 9.27min.

Purity estimated to >99% ee.

LC-MS (APCI) m/z 251.1 (MH+).

$[\alpha]_D$=-30.3° (c=0.01g/mL, MeOH, T=20°C).

^{1}H NMR (DMSO-d_6) δ: 10.74 (1H,s); 8.00 (1H, s); 7.35-7.20 (5H, m); 3.76 (2H, s); 2.72, 2.62 (1H each, ABq, *J*=14.0 Hz); 1.29 (3H, s).

^{13}C NMR (DMSO-d_6) δ: 177.30, 156.28, 138.11, 128.74, 128.24, 126.77, 62.93, 37.96, 36.39, 23.15.

[(4*S*)-4-Methyl-2,5-dioxoimidazolidin-4-yl]methanesulfonyl chloride

(*5S*)-5-Methyl-5-{[(phenylmethyl)thio]methyl}imidazolidine-2,4-dione (42.6g; 0.17mol) was dissolved in a mixture of AcOH (450 mL) and H_2O (50 mL). The mixture was immersed in an ice/water bath, chlorine gas was bubbled through the solution, the flow of gas was adjusted so that the temperature was kept below +15 °C. After 25 minutes the solution became yellow-green in colour and a sample was withdrawn for LC/MS and HPLC analysis. It showed that starting material was consumed. The yellow clear solution was stirred for 30 minutes and an opaque solution /slurry was formed. The solvent was removed on a rotary evaporator using a water-bath with temperature held at 37°C. The yellowish solid was suspended in toluene (400mL) and solvent removed on the same rotary evaporator. This was repeated once more. The crude product was then suspended in iso-hexane (400mL) and warmed to 40°C while stirring, the slurry was allowed to cool to room temperature before the insoluble product was removed by filtration, washed with iso-hexane (6x100mL), and dried under reduced preassure at 50°C overnight. This gave the product as a slightly yellow powder.

Obtained 36.9 g (95%) of the title compound.

Purity by HPLC = 99%, NMR supported that purity.

$[\alpha]_D$=-12.4° (c=0.01g/mL, THF, T=20°C).

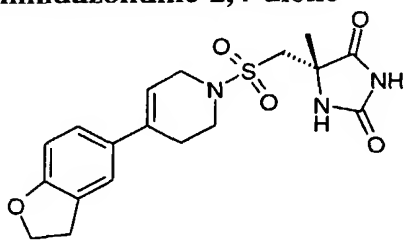
^{1}H NMR (THF-d_8): δ 9.91 (1H, bs); 7.57 (1H, s); 4.53, 4.44 (1H each, ABq, *J*=14.6Hz); 1.52 (s, 3H, CH_3).

^{13}C NMR (THF-d_8): δ 174.96; 155.86; 70.96; 61.04; 23.66.

The following compounds were prepared by methods analogous to the synthesis of 2-methyl-4-[1-({[(4S)-4-methyl-2,5-dioxoimidazolidin-4-yl]methyl}sulfonyl)-1,2,3,6-tetrahydropyridin-4-yl]benzonitrile and its starting materials, and purified either by preparative HPLC or precipitation from EtOH/H_2O.

Example 2

(5*S*)-5-({[4-(2,3-Dihydro-1-benzofuran-5-yl)-3,6-dihydropyridin-1(2*H*)-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione

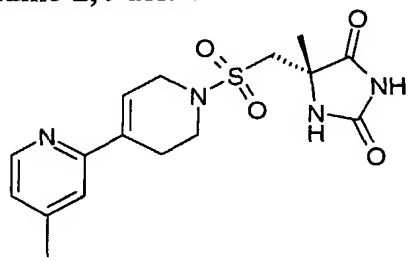


LC-MS (APCI) m/z 392 [MH^+].

^{1}H NMR (DMSO-d_6): δ 10.75 (1H, s); 8.03 (1H, s); 7.33 (1H, s); 7.17 (1H, dd, *J*=8.38, 2.00 Hz); 6.73 (1H, d, *J*=8.39 Hz); 6.03 (1H, bs); 4.52 (2H, t, *J*=8.84 Hz); 3.85-3.80 (2H, m); 3.53, 3.39 (1H each, ABq, *J*=15.57 Hz); 3.17 (2H, t, *J*=8.42 Hz); 1.33 (3H, s).

Example 3

(5*S*)-5-Methyl-5-{[(4-methyl-3',6'-dihydro-2,4'-bipyridin-1'(2'*H*)-yl)sulfonyl]methyl}imidazolidine-2,4-dione

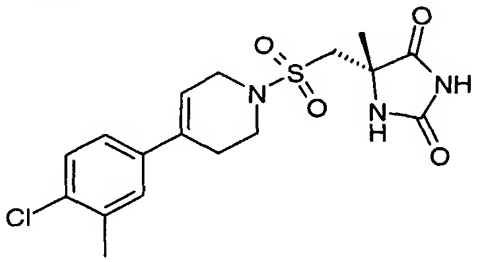


LC-MS (APCI) m/z 365 [MH^+].

^{1}H NMR DMSO-d_6: δ 10.76 (1H, s); 8.49 (1H, d, *J*=5.41 Hz); 8.05 (1H, s); 7.62 (1H, s); 7.37 (1H, d, *J*=5.04 Hz); 6.76 (1H, bs); 3.98-3.92 (2H, m); 3.56, 3.44 (1H each, ABq, *J*=14.98 Hz); 3.40 (2H, t, *J*=5.92 Hz); 2.70-2.64 (2H, m); 2.43 (3H, s); 1.34 (3H, s).

Example 4

(5*S*)-5-({[4-(4-Chloro-3-methylphenyl)-3,6-dihydropyridin-1(2*H*)-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione

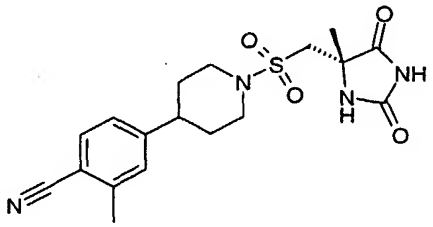


LC-MS (APCI) m/z 398 [MH^+].

^{1}H NMR DMSO-d_6: δ 10.75 (1H, s); 8.03 (1H, s); 7.45 (1H, d, *J*=1.94 Hz); 7.38 (1H, d, *J*=8.30 Hz); 7.29 (1H, dd, *J*=8.30, 1.94 Hz); 6.22 (1H, bs); 3.87-3.83 (2H, m); 3.54, 3.40 (1H each, ABq, *J*=15.11 Hz); 3.37 (2H, t, *J*=6.23 Hz); 2.58-2.52 (2H, m); 2.34 (3H, s); 1.33 (3H, s).

Example 5

2-Methyl-4-[1-({[(4*S*)-4-methyl-2,5-dioxoimidazolidin-4-yl]methyl}sulfonyl)piperidin-4-yl]benzonitrile



LC-MS (APCI) m/z 391 [MH^+].

^{1}H NMR DMSO-d_6: δ 10.74 (1H, s); 8.02 (1H, s); 7.69 (1H, d, *J*=7.99 Hz); 7.39 (1H, s); 7.29 (1H, d, *J*=8.11 Hz); 3.69-3.55 (2H, m); 3.52, 3.34 (1H each, ABq, *J*=14.61 Hz); 2.93-2.81 (2H, m); 2.74-2.63 (1H, m); 2.46 (3H, s); 1.87-1.79 (2H, m); 1.72-1.59 (2H, m); 1.34 (3H, s).

The starting material was prepared as follows:

tert-Butyl 4-(4-cyano-3-methylphenyl)piperidine-1-carboxylate

tert-Butyl 4-(4-cyano-3-methylphenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (171 mg, 0.57 mmol) was dissolved in EtOAc (10 ml), 10% Pd/C (10 mg) added and the mixture was hydrogenated at room temperature and 1 atm for 40 mins. The catalyst was filtered off and the solvent removed by rotary evaporation affording 171 mg (99%) of the title compound as a clear oil.

LC-MS (APCI) m/z 201 [MH^+].

^{1}H NMR $CDCl_3$: δ 7.49 (1H, d, *J*=7.99 Hz); 7.12 (1H, bs); 7.07 (1H, dd, *J*=8.04, 1.71 Hz); 4.22 (2H, d, *J*=11.67 Hz); 2.76 (2H, t, *J*=12.14 Hz); 2.49 (3H, s); 1.77 (2H, d, *J*=12.71 Hz); 1.65-1.48 (2H, m); 1.45 (9H, s).

Pharmacological Example

Isolated Enzyme Assays

Recombinant human MMP12 catalytic domain may be expressed and purified as described by Parkar A.A. *et al*, (2000), Protein Expression and Purification, 20:152. The purified enzyme can be used to monitor inhibitors of activity as follows: MMP12 (50 ng/ml final concentration) is incubated for 60 minutes at room temperature with the synthetic substrate Mac-Pro-Cha-Gly-Nva-His-Ala-Dpa-NH_2 in assay buffer (0.1M "Tris-HCl" (trade mark) buffer, pH 7.3 containing 0.1M NaCl, 20mM $CaCl_2$, 0.020 mM ZnCl and 0.05% (w/v) "Brij 35" (trade mark) detergent) in the presence (5 concentrations) or absence of inhibitors. Activity is determined by measuring the fluorescence at λex 320nm and λem 405nm. Percent inhibition is calculated as follows: % Inhibition is equal to the [$Fluorescence_{plus\ inhibitor}$ - $Fluorescence_{background}$] divided by the [$Fluorescence_{minus\ inhibitor}$ - $Fluorescence_{background}$].

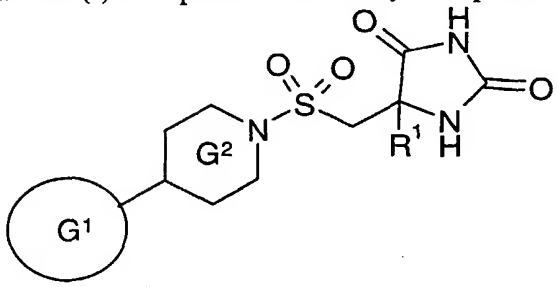
A protocol for testing against other matrix metalloproteinases, including MMP9, using expressed and purified pro MMP is described, for instance, by C. Graham Knight *et al.*, (1992) FEBS Lett. 296(3):263-266.

The following table shows the IC_{50} figures (in nanomolar) for the compounds of the examples when tested against MMP12 and MMP9.

Compound of Example No.	**Human MMP12 IC_{50} (nm)**	**Human MMP9 IC_{50} (nm)**
1	0.26	15.00
2	1.20	22.00
3	4.60	6.80
4	0.41	13.00
5	1.40	39.00

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof



(I)

wherein

R^1 represents hydrogen, or a group selected from C_1-C_6 alkyl and a saturated or unsaturated 3- to 10-membered ring system which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each group being optionally substituted with at least one substituent selected from halogen, hydroxyl, cyano, carboxyl, $-NR^2R^3$, $-CONR^4R^5$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylcarbonyl(oxy), $-S(O)_mC_1$-C_6 alkyl where m is 0, 1 or 2, C_1-C_6 alkylsulphonylamino, C_1-C_6 alkoxycarbonyl(amino), benzyloxy and a saturated or unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring in turn being optionally substituted with at least one substituent selected from halogen, hydroxyl, oxo, carboxyl, cyano, C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl and C_1-C_6 hydroxyalkyl;

R^2, R^3, R^4 and R^5 each independently represent hydrogen or C_1-C_6 alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy;

G^2 represents a piperidine or a tetrahydropyridine ring;

G^1 represents a 5- or 6- membered aryl or heteroaryl monocyclic ring which may be optionally fused to a second ring to form a bicyclic ring system containing a total of 8- to 10-ring atoms, the monocyclic ring or fused bicyclic ring system being optionally substituted with at least one substituent selected from halogen, hydroxyl, cyano, nitro, C_1-C_6 alkyl (optionally substituted by one or more of cyano, halogen, hydroxyl and

methoxy), C_2-C_6 alkenyl, C_1-C_6 alkoxy (optionally substituted by one or more halogen atoms), -$S(O)_n$$C_1$-$C_6$ alkyl where n is 0, 1 or 2 (optionally substituted by one or more halogen atoms), C_1-C_6 alkylcarbonyl(amino), C_1-C_6 alkylcarbonyloxy, phenyl, benzyloxy and $-NR^6R^7$; and

R^6 and R^7 each independently represent hydrogen or C_1-C_6 alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy.

2. A compound according to claim 1, wherein R^1 represents hydrogen, or a group selected from C_1-C_4 alkyl and a saturated or unsaturated 5- to 10-membered ring system which may comprise one, two, three or four ring heteroatoms independently selected from nitrogen, oxygen and sulphur, each group being optionally substituted with one, two, three or four substituents independently selected from halogen, hydroxyl, cyano, carboxyl, $-NR^2R^3$, $-CONR^4R^5$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylcarbonyl(oxy), -$S(O)_m$$C_1$-$C_4$ alkyl where m is 0, 1 or 2, C_1-C_4 alkylsulphonylamino, C_1-C_4 alkoxycarbonyl(amino), benzyloxy and a saturated or unsaturated 5- to 6-membered ring which may comprise one, two, three or four ring heteroatoms independently selected from nitrogen, oxygen and sulphur, the ring in turn being optionally substituted with one, two or three substituents independently selected from halogen, hydroxyl, oxo, carboxyl, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxycarbonyl and C_1-C_4 hydroxyalkyl.

3. A compound according to claim 1 or claim 2, wherein R^1 represents hydrogen or C_1-C_4 alkyl.

4. A compound according to any one of claims 1 to 3, wherein G^2 represents a tetrahydropyridine ring.

5. A compound according to any one of claims 1 to 4, wherein G^1 represents a 5- or 6-membered aryl or heteroaryl monocyclic ring optionally substituted in a *meta* and/or *para* position.

6. A compound according to claim 5, wherein the *meta* substituent is selected from C_1-C_3 alkyl and $-CH_2CN$.

7. A compound according to claim 5, wherein the *para* substituent is selected from Br, Cl, -CN, $-CF_3$, $-SCF_3$ and $-OCF_3$.

8. A compound according to any one of claims 1 to 4, wherein, in G^1, the bicyclic ring system is selected from quinolinyl, isoquinolinyl, indolyl, tetrahydroisoquinolinyl, benzofuranyl, dihydrobenzofuranyl, naphthyl and dihydroindolyl.

9. A compound according to claim 1 which is selected from the group consisting of:

2-Methyl-4-[1-({[(4*S*)-4-methyl-2,5-dioxoimidazolidin-4-yl]methyl}sulfonyl)-1,2,3,6-tetrahydropyridin-4-yl]benzonitrile,

(5*S*)-5-({[4-(2,3-Dihydro-1-benzofuran-5-yl)-3,6-dihydropyridin-1(2*H*)-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione,

(5*S*)-5-Methyl-5-{[(4-methyl-3',6'-dihydro-2,4'-bipyridin-1'(2'*H*)-yl)sulfonyl]methyl}imidazolidine-2,4-dione,

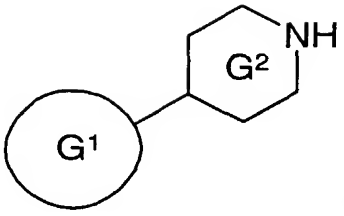
(5*S*)-5-({[4-(4-Chloro-3-methylphenyl)-3,6-dihydropyridin-1(2*H*)-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione,

2-Methyl-4-[1-({[(4*S*)-4-methyl-2,5-dioxoimidazolidin-4-yl]methyl}sulfonyl)piperidin-4-yl]benzonitrile,

and pharmaceutically acceptable salts and solvates thereof.

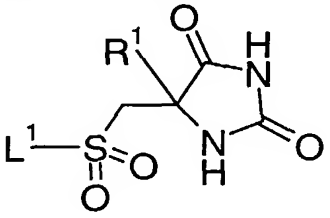
10. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as defined in claim 1 which comprises,

(a) reacting a compound of formula



(II)

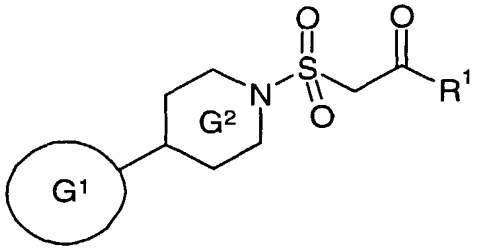
in which G^1 and G^2 are as defined in formula (I), with a compound of formula



(III)

wherein L^1 represents a leaving group and R^1 is as defined in formula (I); or

(b) reacting a compound of formula



(IV)

wherein R^1, G^1 and G^2 are as defined in formula (I), with potassium cyanide and ammonium carbonate;

and optionally after (a) or (b) forming a pharmaceutically acceptable salt or solvate.

11. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 9 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

12. A process for the preparation of a pharmaceutical composition as claimed in claim 11 which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as defined in any one of claims 1 to 9 with a pharmaceutically acceptable adjuvant, diluent or carrier.

13. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 9 for use in therapy.

14. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 9 in the manufacture of a medicament for use in the treatment of an obstructive airways disease.

15. Use according to claim 14, wherein the obstructive airways disease is asthma or chronic obstructive pulmonary disease.

16. A method of treating a disease or condition mediated by MMP12 and/or MMP9 which comprises administering to a patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 9.

17. A method of treating an obstructive airways disease which comprises administering to a patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 9.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/001407

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 401/12, C07D 401/14, C07D 405/14, A61K 31/4523, A61K 31/4427, A61P 11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02074750 A1 (ASTRAZENECA AB), 26 Sept 2002 (26.09.2002) --	1-17
P,X	WO 02074767 A1 (ASTRAZENECA AB), 26 Sept 2002 (26.09.2002) --	1-17
A	EP 1191024 A1 (TSCHESCHE, HARALD), 27 March 2002 (27.03.2002) -- --------	1-17

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 January 2004	13 -01- 2004
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Solveig Gustavsson/BS Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2003/01407

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 16-17
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claims 16-17 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule. 39.1.(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/12/2003

International application No.
PCT/SE 2003/001407

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02074750 A1	26/09/2002	AU 5282101 A	26/11/2001
		CA 2440473 A	26/09/2002
		NO 20034025 D	00/00/0000
		NO 20034042 D	00/00/0000
		NO 20034044 D	00/00/0000
		NO 20034045 D	00/00/0000
		SE 0100902 D	00/00/0000
		WO 02074748 A	26/09/2002
		WO 02074751 A	26/09/2002
		WO 02074767 A	26/09/2002
		AU 5282201 A	12/11/2001
		CA 2440475 A	26/09/2002
		NO 20034027 D	00/00/0000
		NO 20034032 D	00/00/0000
		SE 0100903 D	00/00/0000
		WO 02074749 A	26/09/2002
		WO 02074752 A	26/09/2002
WO 02074767 A1	26/09/2002	AU 5282101 A	26/11/2001
		CA 2440473 A	26/09/2002
		NO 20034025 D	00/00/0000
		NO 20034042 D	00/00/0000
		NO 20034044 D	00/00/0000
		NO 20034045 D	00/00/0000
		SE 0100902 D	00/00/0000
		WO 02074748 A	26/09/2002
		WO 02074750 A	26/09/2002
		WO 02074751 A	26/09/2002
EP 1191024 A1	27/03/2002	NONE	